Review

Hepatic encephalopathy: Part 2, inpatient management

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ABSTRACT

The second of this four-part review encompasses the inpatient management of hepatic encephalopathy (HE) in patients with decompensated cirrhosis, acute-on-chronic liver failure (ACLF) and acute liver failure (ALF). The management of overt HE in cirrhosis consists of excluding alternative causes of altered mental state, identifying and correcting precipitants, instigating nutritional support and initiating pharmacological therapy. The presence of HE in combination with other organ failures defines ACLF, and these patients are frequently managed in the intensive care setting. Aside from the treatment of precipitants and organ support in ACLF, there is an emerging role for emergency liver transplantation in highly selected patients. ALF is characterised by the development of severe hepatocellular injury accompanied by coagulopathy and HE, in patients usually without pre-existing chronic liver disease. The often rapid development of hyperammonaemia in ALF may culminate in cerebral oedema and intracranial hypertension, which is specific to this syndrome and, as such, management of HE in ALF differs from that in cirrhosis. A package of neuroprotective care is delivered, including specific monitoring for cerebral oedema, and osmotic therapy is employed for surges in intracranial pressure. Specific ammonia-lowering therapies recommended include continuous renal replacement therapy and therapeutic plasma exchange, with emergency liver transplantation the definitive treatment in the absence of liver regeneration and spontaneous recovery. Independent of underlying aetiology, patients with grade 3–4 HE should be managed in the intensive care unit due to risk of airway compromise and aspiration.

KEY MESSAGES

⇒ The inpatient management of overt hepatic encephalopathy (HE) in cirrhosis requires a multifaceted approach; excluding alternative causes for altered mental status, identifying and correcting precipitants, ensuring adequate nutrition and initiating pharmacological therapy.
⇒ Acute-on-chronic liver failure describes the development of one or more organ failures, including HE, following an acute insult that is either hepatic or extrahepatic, in the setting of decompensated cirrhosis.
⇒ HE is an essential component of acute liver failure, where cerebral oedema and intracranial hypertension are unique to this syndrome.
⇒ Patients with grade 3–4 HE, independent of underlying aetiology, should be managed in the intensive care unit with airway protection.

INTRODUCTION

Hepatic encephalopathy (HE) accounts for a significant proportion of hospital admissions (35%) in patients with cirrhosis and is a principal cause of readmission (45%) in this patient cohort.[1] The advent of overt HE is debilitating and, out of all decompensating events, carries the highest 1-year mortality at 64%.[2] While HE can occur as an index decompensation in patients with cirrhosis (10–15%),[2] it often occurs in combination with other decompensating events, and there are a number of common precipitating factors. The development of HE in acutely decompensated cirrhosis in conjunction with other organ failures defines acute-on-chronic liver failure (ACLF).[3 4] As such, the inpatient management of HE in cirrhosis stretches beyond medications targeted to actively treat HE and requires a multipronged approach.[5 6] This consists of: excluding alternative causes of altered mental state, identification and treatment of precipitating risk factors (as covered in *Part 1*),[7] ensuring adequate nutrition and initiating pharmacological therapy.

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Acute liver failure (ALF) is characterised by the presence of HE, together with coagulopathy and hepatocellular injury, in patients without pre-existing liver disease.[8 9] Consequently, the management of HE in ALF differs from that in cirrhosis, although many treatment principles are similar. In all cases, grade 3–4 HE should be identified promptly and managed in the intensive care unit (ICU) due to risk of airway compromise.[5 8]

ACUTE OVERT HE IN CIRRHOSIS

General inpatient management principles

Once a diagnosis of overt HE is suspected, covered comprehensively in *Part 1*[7] of this review series, it is critical to identify and correct precipitating factors, present in the vast majority of cases,[5 6] since specific treatments of HE are unlikely to be successful without precipitating factor resolution. Once such factors have been treated, up to 90% of patients can be expected to recover from an episode of overt HE within 48 hours,[5 10] though it is unclear if this improves long-term prognosis. Infection is the most common precipitating factor and is associated with increased mortality,[11 12] thus requiring timely antimicrobial treatment. Further common precipitants include constipation, gastrointestinal bleeding, hypovolaemia, hyponatraemia and medications.[13 14] Prompt removal of blood from the gastrointestinal tract[15] and resolution of constipation[16 17] improve recovery from an episode of overt HE. Electrolyte correction, intravenous fluid rehydration,[18] withdrawal of diuretic therapy and avoidance of sedating medications should be employed where indicated.[5] CT head should be performed in new or worsening overt HE, to exclude concomitant intracranial pathology.[7 8] HE should be graded daily, as per the West Haven Criteria (WHC), to assess response to treatment.[19]

Transfer to a critical care setting and airway protection through endotracheal intubation is recommended for patients with grade 3–4 HE, which equates to a Glasgow Coma Score (GCS) ≤8.[5] Overt HE is, in theory, fully reversible[5] and thus should not be considered a contraindication to ICU admission. The approach to ICU management of overt HE is covered in the subsequent section on ACLF, and figure 1 depicts the inpatient management of grade 1/2 versus grade 3/4 HE.

Steps should be taken to prevent readmission with HE prior to discharge. This includes patient and

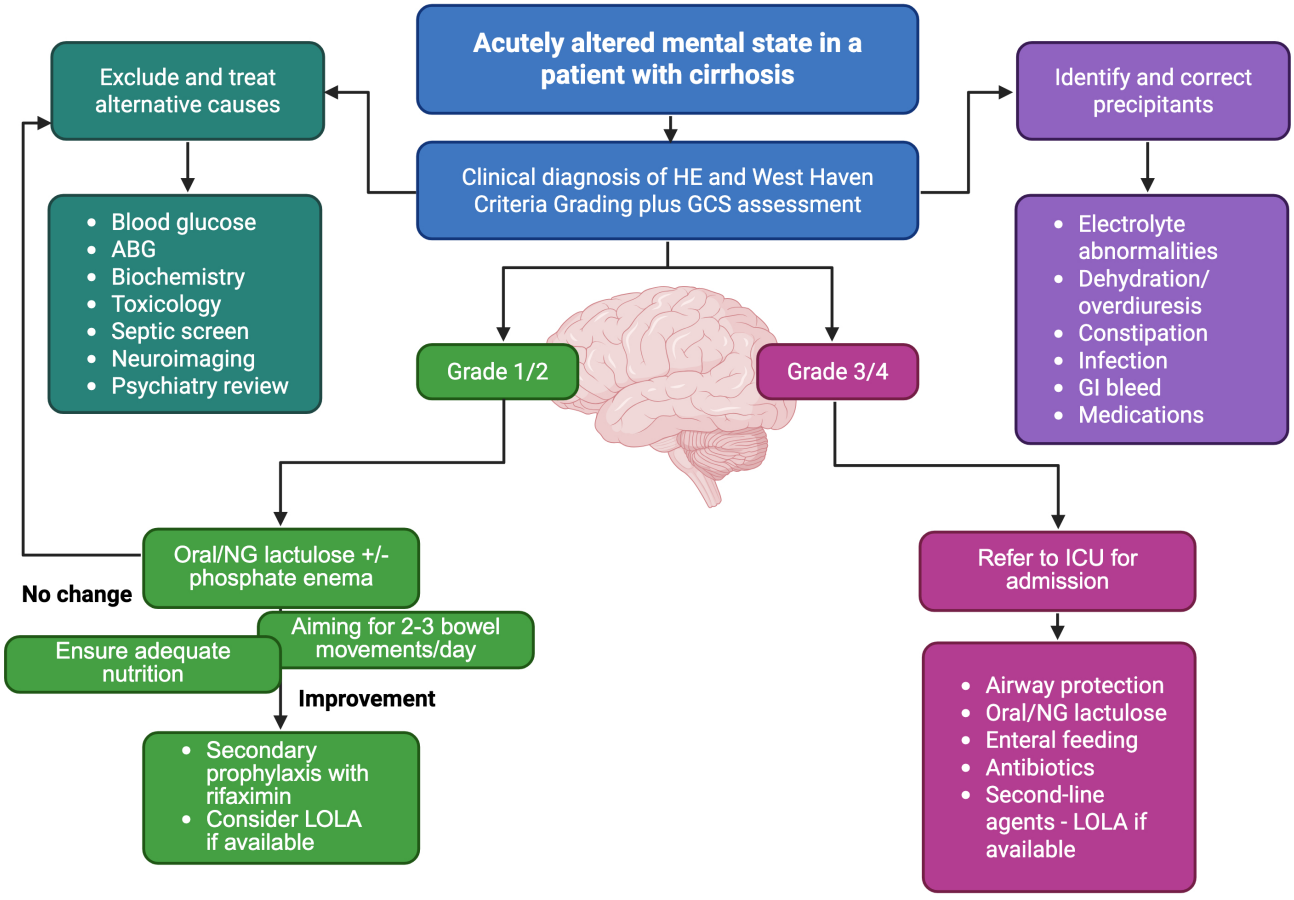

Figure 1 Management algorithm for grade 1–2 versus grade 3–4 hepatic encephalopathy in cirrhosis. Created with *Biorender.com*. ABG, arterial blood gas; GCS, Glasgow Coma Scale; GI, gastrointestinal; HE, hepatic encephalopathy; ICU, intensive care unit; LOLA, L-Ornithine-L-Aspartate; NG, nasogastric.

caregiver training on HE and provision of healthcare provider-recommended educational resources.[20] Patients should also be advised to carry an alert card or medical bracelet to ensure healthcare providers are aware of the diagnosis of HE in an emergency.[21]

Nutritional support

Cirrhosis is a catabolic state, in which muscle protein breakdown exceeds synthesis, which results in sarcopenia.[22] Skeletal muscle plays a key role in the detoxification of circulating ammonia, thus patients with reduced muscle mass are at higher risk of developing HE. In addition, chronic hyperammonaemia causes activation of myostatin, limiting muscle protein synthesis and contributing to further muscle wasting.[19] It is therefore essential to optimise nutritional status in patients admitted with HE. Patients should be maintained on high energy (30–35 kcal/kg/day), high protein (1.2–1.5 g/kg/day) diets[23] with the avoidance of daytime fasting for longer than 3–6 hours and should consume a bedtime snack.[24] Referral to a dietician to ensure adequate calorie and protein requirements are met is associated with lower 90-day readmission rates in patients with cirrhosis.[25]

There is no compelling evidence that the use of fine bore nasogastric tubes for enteral feeding should be avoided in patients with oesophageal varices,[26–28] and enteral nutrition should be provided to patients who cannot meet their nutritional requirements through oral diet and/or supplementation.[29] Any demonstrated or suspected vitamin and micronutrient deficiencies such as thiamine or zinc should be treated, as they can compound HE. If Wernicke's encephalopathy is suspected, high-dose parenteral thiamine supplementation is obligatory.[5]

Specific anti-HE medications

Lactulose, a non-absorbable disaccharide, remains the first line treatment for pharmacological management of overt HE[5] and is the only anti-HE drug that confers a survival benefit when used alone.[30] Its hyperosmolar laxative effect increases stool frequency which reduces ammonia absorption and increases removal of nitrogenous compounds. Furthermore, acidic breakdown products of lactulose favour conversion of free ammonia to non-absorbable ammonium ions. Lactulose also acts as a prebiotic for beneficial non-urease producing gut microbiota, such as *Lactobacillus*.[31] It should be commenced at a dose of 20-30 mL four times a day in overt HE, aiming for two to three soft stools per day.[32] Regular laxative dosage until improvement in HE is associated with reduced length of hospital stay in non-randomised trials.[33] Phosphate enemas can be used for a more instantaneous result, especially when the precipitant is constipation, given that lactulose can take 48 hours to establish optimal effect. When combined with polyethylene glycol (PEG-3350), time to improved mental status is shortened.[34 35] Lactulose has also been shown to significantly reduce the incidence of HE in patients with gastrointestinal bleeding, though without survival benefit.[36–38]

Rifaximin, a minimally absorbable broad-spectrum antibiotic, should be used as an adjunct to lactulose as secondary prophylaxis in those who have had two or more episodes of overt HE within 6 months.[5] It has proven efficacy in maintaining HE remission and reducing hospitalisation risk in HE,[39] though it has little role in the acute inpatient management of overt HE,[40] where bacterial infection is a frequent precipitant and broad spectrum antibiotics are administered parenterally. On meta-analysis, rifaximin reduced overall mortality and reduced length of hospital stay, only when added to lactulose.[41]

L-Ornithine-L-Aspartate (LOLA), a combination of two endogenous amino acids, stimulates hepatic urea synthesis and skeletal muscle glutamine synthesis, reducing ammonia levels. While its use remains unlicensed, meta-analyses have demonstrated that LOLA improves mental state in both covert and overt HE.[42]

Oral LOLA sachets are typically commenced at 5 g (3 g active ingredient) two times per day and uptitrated to a maximum of 10 g three times a day according to response. The standard LOLA intravenous infusion loading dose is 20 g over 4 hours, followed by a continuous 20 g infusion over 24 hours, for a maximum of 5 days.

Liver transplantation (LT) is the definitive treatment for HE. However, patients with overt HE and cirrhosis cannot be listed for emergency LT, unless in the setting of ACLF,[43 44] but require stabilisation, treatment of the decompensation event and consideration of LT on recovery.

ACUTE-ON-CHRONIC LIVER FAILURE

Definition

ACLF reflects the development of one or more organ failures following an acute hepatic or extrahepatic insult, in the setting of acutely decompensated cirrhosis and carries a high short-term mortality at 28 days of greater than 20%.[3] ACLF is characterised by an excessive systemic inflammatory response, most commonly triggered by acute precipitants such as bacterial infection or severe alcohol-associated hepatitis, and is graded based on the number of organ failures present (liver, kidney, acute encephalopathy, coagulation, respiration, circulation).[3 4 45]

While a number of definitions for ACLF exist, the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium (CLIF-C) is widely accepted (table 1).[3] Organ failure definitions, included in the EASL-CLIF-C criteria, are used;[3] however, updated organ failure definitions for patients with cirrhosis have recently been proposed in a consensus statement.[4]

Patients with ACLF frequently require admission to ICU for intensive monitoring and organ support.

Table 1 EASL-CLIF definition and grading of acute-on-chronic liver failure. Adapted from Moreau *et al*[3]

Grade	Clinical characteristics	28-day mortality
No ACLF	No organ failure, or single non-kidney organ failure, creatinine <1.5 mg/dL, no HE	–
ACLF Ia	Single renal failure (creatinine >2 mg/dL)	22%
ACLF Ib	Single liver, coagulation, circulatory or respiratory failure plus creatinine 1.5–1.9 mg/dL and/or HE grade 1 or 2	
ACLF II	Two organ failures	32%
ACLF III	Three or more organ failures	77%

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

Despite initial concern that patients with ACLF have a high mortality despite intensive management, recent developments have demonstrated improved survival of patients with ACLF admitted to ICU.[46] In a matched ICU population without cirrhosis and the same critical illness severity, patients with ACLF had a similar ICU length of stay and mortality rate.[47] Criteria for ICU admission for patients with ACLF should therefore be similar to those used in other critically unwell patient populations.

Acute encephalopathy and overt hepatic encephalopathy

While the term 'brain failure' was previously used to describe one of the organ failures in ACLF,[48] it does not refer to a pathophysiological process and the term 'acute encephalopathy' is now preferred.[5 49] The most common cause of neurological dysfunction and altered mental status in patients with ACLF is HE; however, acute encephalopathy can also be caused by a number of other differentials, such as central nervous system infection, metabolic abnormalities and drug effects (see *Part 1*).[7] HE in ACLF is most likely the result of the accumulation of circulating toxins, namely ammonia, coupled with marked systemic inflammation[50] and is associated with increased mortality independent of other organ failures.[51]

ICU management of HE

The ICU approach to overt HE, applicable to decompensated cirrhosis and ACLF, is standardised; airway protection with endotracheal intubation is required for patients with WHC Grade 3 or 4 HE.[52] Sedating agents should be kept to a minimum where possible, especially in those intubated for a depressed mental state only, to allow for frequent neurocognitive assessments and early extubation.[53] For patients who require mechanical ventilation for respiratory failure, short-acting agents such as propofol are considered first-line.[52] Dexmedetomidine, a highly selective alpha 2 adrenergic agonist, has also been used in this setting and is associated with preserved cognitive function and decreased duration of ventilation.[54 55] Benzodiazepines should be avoided as they can worsen neurocognitive impairment in cirrhosis.[56] A nasogastric tube should be used for those who cannot swallow, have risk of aspiration or are intubated, and enteral feeding should be commenced.[23]

Alternative and synergistic causes of altered mental status, alongside precipitating factors for HE and ACLF, should be recognised and treated. Patients with ACLF are at increased risk of stroke, predominantly intracranial haemorrhage (especially in those with alcohol-related cirrhosis)[57] and therefore clinicians should have a low threshold for cerebral imaging. Electroencephalogram (EEG) may be considered in patients who do not respond to standard treatment.[58] The data on blood ammonia measurement is variable; however, a low or normal ammonia level in patients with altered mental status and ACLF suggests alternative causes for acute encephalopathy other than HE.[59] Furthermore, several studies have demonstrated the prognostic utility of ammonia in ACLF, with ammonia independently predicting mortality in this cohort.[60–62]

Data supporting ICU use of most drugs employed for overt HE in other clinical settings remains limited.[5] Lactulose is the first-line treatment for overt HE as previously discussed. In patients who cannot take lactulose orally, it can be administered via nasogastric tube or as a retention enema.[58] However, excessive dosing can lead to hypovolaemia and electrolyte disturbances, which can worsen HE, and lactulose may need to be held if ileus develops.[63]

The optimal second-line agent in this setting remains to be determined. Antibiotics, including rifaximin, PEG-3350,[35] oral branched-chain amino acids, intravenous LOLA[64–66] and probiotics have all been evaluated.[5 67] A recent randomised controlled trial (RCT) of critically ill patients with cirrhosis admitted to ICU found no benefit of adding rifaximin to broad spectrum antibiotics in the reversal of overt HE, or on mortality in those with ACLF.[40] Intravenous LOLA, in conjunction with lactulose and rifaximin, has been shown to be more effective at reducing HE grade, recovery time from HE episode and 28-day mortality in cirrhotic patients with Grade 3–4 HE, compared with lactulose and rifaximin alone.[66] A recent RCT further established the ammonia lowering effects and beneficial treatment effect on HE, demonstrated by a reduction in HE grade, of both oral and intravenous LOLA when used alongside lactulose and rifaximin in

patients with cirrhosis and overt HE.[68] While cerebral oedema and intracranial hypertension (ICH) do not pose a significant clinical issue in ACLF,[69] the ammonia lowering role of continuous renal replacement therapy (CRRT) to reduce time to resolution of HE requires further exploration.[70]

Albumin-based dialysis therapies, such as molecular adsorbent recirculating system (MARS) and Prometheus, have been shown to decrease serum bilirubin levels and reduce HE severity in ACLF, but with no impact on survival,[71 72] and current use is limited to investigative trials.[73] The impact of therapeutic plasma exchange (TPE) on transplant-free survival is currently being assessed in patients with ACLF, through the phase III multicentre APACHE (Short-term Survival of Subjects with Acute-on-chronic Liver Failure after Plasma Exchange with Human Serum Albumin 5%) RCT (NCT03702920), with previous studies reporting encouraging results.[74]

Liver transplantation for ACLF

There was initial hesitation regarding LT for ACLF, due to high wait-list mortality, previously reported poor outcomes for ACLF grade 3[74] and high resource use. However, recent studies,[75] including the pilot ACLF tier for LT in the UK,[44] have demonstrated acceptable outcomes, with 77% 1-year post LT survival in highly selected patients. As per the latest EASL Clinical Practice Guidelines for LT (2024),[43] patients with ACLF grade 3 should be considered for LT evaluation, which leads to resolution of HE in most cases, though it should be noted that the window for successful LT is extremely narrow.

ACUTE LIVER FAILURE

ALF is a rare life-threatening syndrome, with a UK incidence of 1–8 per million population,[76] characterised by the development of severe hepatocellular injury accompanied by coagulopathy (international normalised ratio >1.5) and HE, in patients usually without pre-existing chronic liver disease.[8] Patients with ALF may spontaneously recover with supportive treatment, or may progress to refractory multiorgan failure and death. Emergency LT remains the most effective treatment, given inadequate efficacy of currently available liver support systems.[70]

While the pathophysiological mechanisms behind liver injury in ALF vary by aetiology, the end result is massive hepatocyte necrosis leading to loss of hepatic metabolic and immunological function.[76] The failing liver is unable to convert ammonia to urea, leading to toxic accumulation.[77] The main causes of death in ALF are sepsis with multiorgan failure and complications of cerebral oedema, though the latter is becoming increasingly uncommon.[78 79]

Aetiology, classification and prognostication

Paracetamol-induced hepatotoxicity, usually after overdose, is the leading cause of ALF in the UK. Other aetiologies include autoimmune hepatitis, viral hepatitis and drug-induced liver injury, while a substantial proportion remain indeterminate[80] and leading cause depends on geographical location.

ALF is classified as hyperacute, acute or subacute, depending on the interval between the development of jaundice and onset of HE (see table 2).[76] This classification is clinically important, as it can aid with diagnosis, resultant complications and prognostication.

A comprehensive diagnostic approach to determine the cause of ALF is important, to ensure timely specific aetiological treatments and/or any contraindications to emergency LT (detailed in figure 2).[8]

ALF progression, especially hyperacute, is inconsistent. Thus, once ALF has developed, rapid admission to the ICU and discussion with a specialist LT centre is indicated, as even without LT, survival is improved in specialised centres.[71] Table 3 denotes suggested criteria for transfer to a specialist LT centre.

HE in ALF

HE is an essential component of ALF and can progress rapidly to coma. Diagnosis is clinical and exclusion of the usual differential causes of altered mental state is again required (see *Part 1*).[7] The progression of HE

Table 2 Classification and clinical features of acute liver failure, as per O'Grady *et al*[127] and Ichai and Samuel.[128] Adapted from Bernal *et al*[76]

	Hyperacute	Acute	Subacute
Time from jaundice to encephalopathy	0–1 week	1–4 weeks	4–12 weeks
Severity of coagulopathy	+++	++	+
Severity of jaundice	+	++	+++
Risk of intracranial hypertension	++	+	±
Survival rate without emergency LT	Good	Moderate	Poor
Typical aetiology	Paracetamol, hepatitis A, hepatitis E	Hepatitis B	Non-paracetamol drug-induced liver injury, seronegative hepatitis

+++ = high severity, ++ = medium severity, + = low severity, ± = present or absent.
LT, liver transplantation.

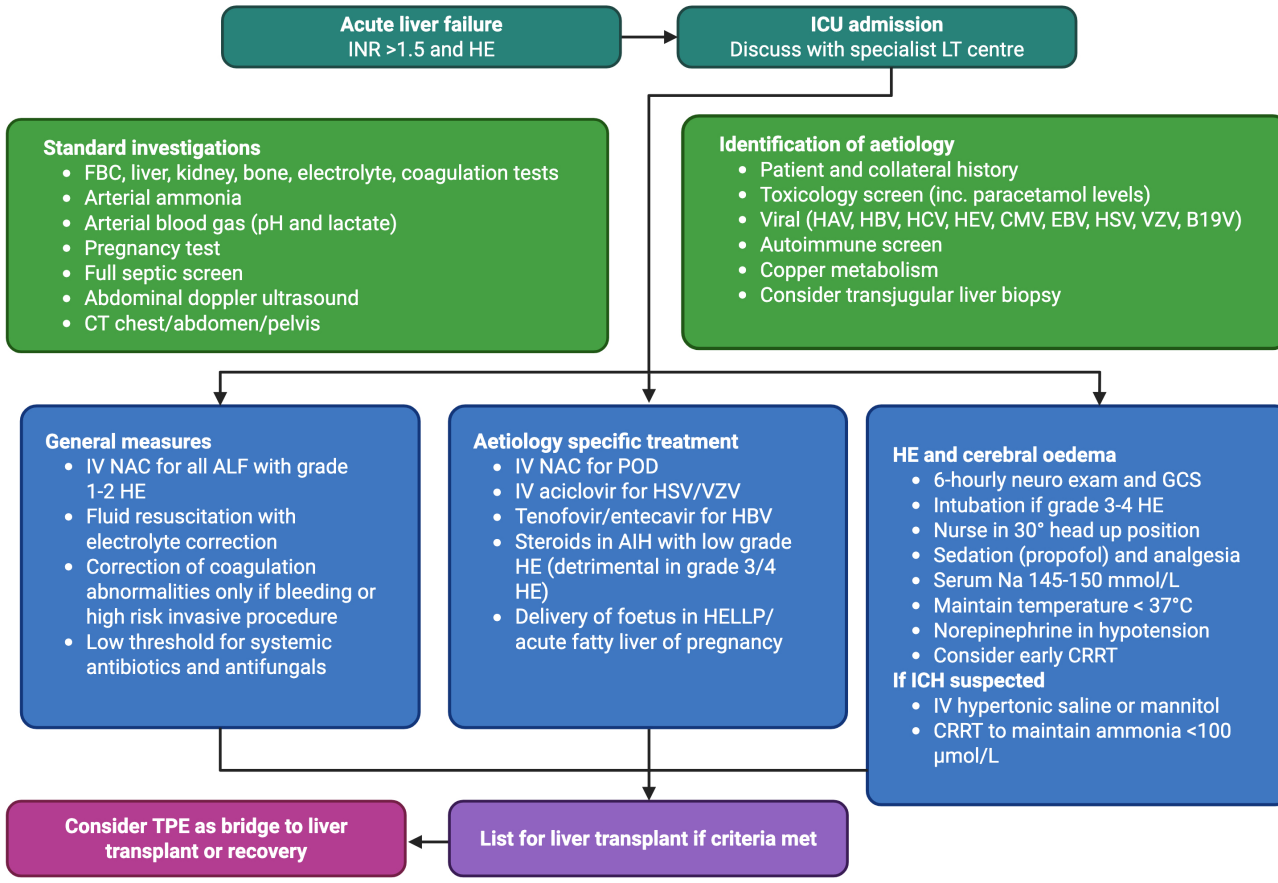
Acute liver failure
INR >1.5 and HE
ICU admission
Discuss with specialist LT centre
Standard investigations
FBC, liver, kidney, bone, electrolyte, coagulation tests
Arterial ammonia
Arterial blood gas (pH and lactate)
Pregnancy test
Full septic screen
Abdominal doppler ultrasound
CT chest/abdomen/pelvis
Identification of aetiology
Patient and collateral history
Toxicology screen (inc. paracetamol levels)
Viral (HAV, HBV, HCV, HEV, CMV, EBV, HSV, VZV, B19V)
Autoimmune screen
Copper metabolism
Consider transjugular liver biopsy
General measures
IV NAC for all ALF with grade 1-2 HE
Fluid resuscitation with electrolyte correction
Correction of coagulation abnormalities only if bleeding or high risk invasive procedure
Low threshold for systemic antibiotics and antifungals
Aetiology specific treatment
IV NAC for POD
IV aciclovir for HSV/VZV
Tenofovir/entecavir for HBV
Steroids in AIH with low grade HE (detrimental in grade 3/4 HE)
Delivery of foetus in HELLP/ acute fatty liver of pregnancy
HE and cerebral oedema
6-hourly neuro exam and GCS
Intubation if grade 3-4 HE
Nurse in 30° head up position
Sedation (propofol) and analgesia
Serum Na 145-150 mmol/L
Maintain temperature < 37°C
Norepinephrine in hypotension
Consider early CRRT
If ICH suspected
IV hypertonic saline or mannitol
CRRT to maintain ammonia <100 µmol/L
Consider TPE as bridge to liver transplant or recovery
List for liver transplant if criteria met

Figure 2 Management of acute liver failure. Created with *Biorender.com*. AIH, autoimmune hepatitis; ALF, acute liver failure; B19V, parvovirus B-19; CMV, cytomegalovirus; CRRT, continuous renal replacement therapy; EBV, Epstein-Barr virus; FBC, full blood count; GCS, Glasgow Coma Scale; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HELLP, haemolysis, elevated liver enzymes, low platelets; HSV, herpes simplex virus; HEV, hepatitis E virus; ICH, intracranial hypertension; ICU, intensive care unit; INR, international normalised ratio; IV, intravenous; LT, liver transplantation; Na, sodium; NAC, N-acetyl cysteine; POD, paracetamol overdose; TPE, therapeutic plasma exchange; VZV, varicella zoster virus.

usually occurs in parallel with deterioration in other liver synthetic function parameters.[8] Regular neurological examination is required to detect early HE and progression to grade 3–4 HE, and therefore such patients should be managed in an appropriate clinical environment (level 2 or level 3 care setting).[8] The development of grade 3–4 HE necessitates intubation and ventilation.[8 81] All patients requiring ventilation are sedated, most commonly with propofol and an opiate such as fentanyl.

Table 3 Recommended criteria for transfer of patients with ALF to a specialist LT centre[8]

Paracetamol	Non-paracetamol
Arterial pH <7.30 or HCO_3 <18 mmol/L	Arterial pH <7.30 or HCO_3 <18 mmol/L
INR >3.0 on day 2 or >4.0 thereafter	INR >1.8
Oliguria and/or elevated creatinine	Oliguria/renal failure or Na <130 mmol/L
Altered level of consciousness	Encephalopathy, hypoglycaemia or metabolic acidosis
Hypoglycaemia	Bilirubin>300 µmol/L
Raised arterial lactate unresponsive to fluid	Shrinking liver size

ALF, acute liver failure; HCO_3, bicarbonate; INR, international normalised ratio; LT, liver transplantation; Na, sodium.

Invasive and non-invasive monitoring of cerebral oedema

Cerebral oedema is a grave consequence of ALF and may lead to the development of ICH, which ultimately results in brain stem compression causing ischaemia, haemorrhage and death.[82]

While less common now, ICH occurs in perhaps 30% of cases of severe ALF.[83] Though not fully defined, ammonia is central to the pathogenesis of cerebral oedema in ALF.[84–86] Hyperammonaemia leads to astrocyte swelling, which is the most consistent neuropathological finding in ALF,[84] while systemic inflammation is also contributory (see figure 3).[85]

Clinical and neurological examination, including GCS assessment, should be evaluated a minimum of 6-hourly to detect signs indicative of impending raised intracranial pressure (ICP). In patients with grades 3–4 HE may develop spasticity with extensor posturing,

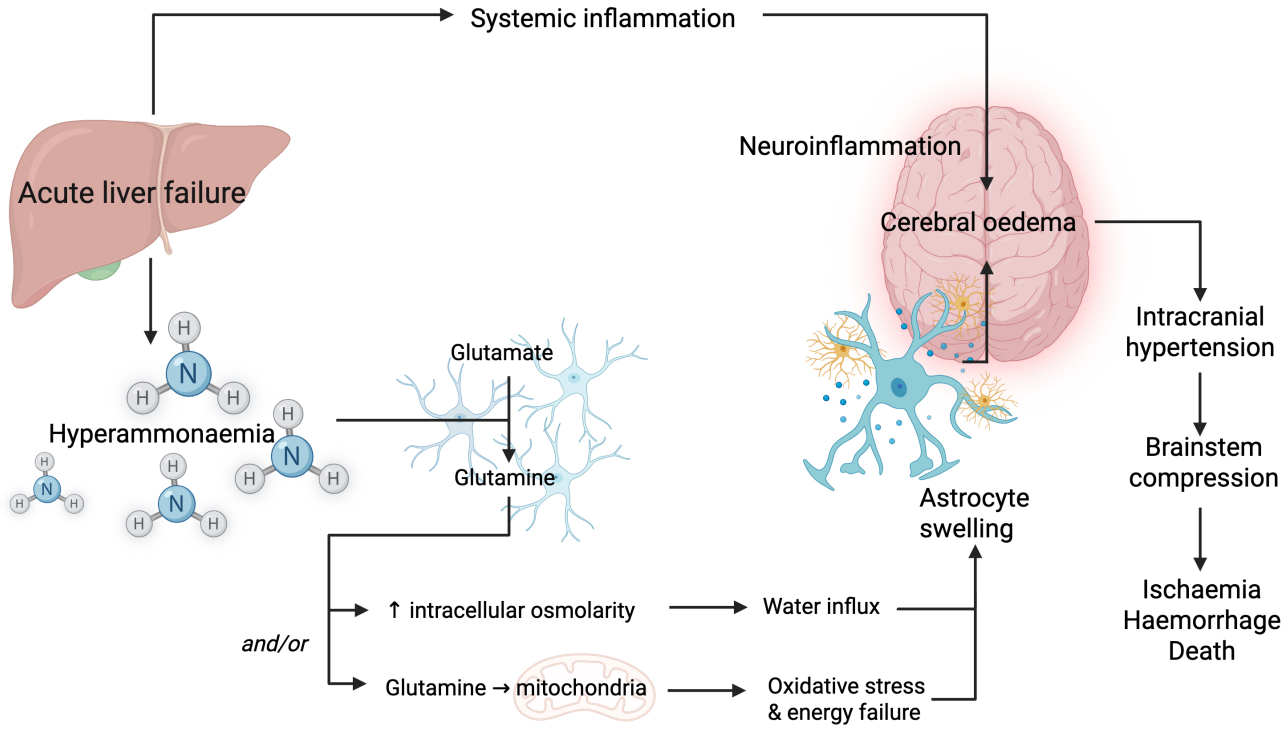

Figure 3 The development of cerebral oedema in acute liver failure. The urea cycle is impaired in acute liver failure due to loss of hepatocyte function, leading to circulating hyperammonaemia. Ammonia enters the brain by diffusion and is detoxified to glutamine, a precursor for the neurotransmitter glutamate, within the astrocyte. Initial hypotheses focused on the role of glutamine as an organic osmolyte, increasing intracellular osmolarity resulting in an influx of water and astrocyte swelling.[77] Current evidence also supports an alternate hypothesis, whereby excess glutamine is transported into mitochondria, acting as a carrier for ammonia (the 'Trojan horse' hypothesis), which results in oxidative stress, energy failure and astrocyte swelling.[86] Acute liver failure triggers profound systemic inflammation which, in conjunction with astrocyte swelling, results in cerebral oedema. Cerebral oedema can lead to intracranial hypertension which, if untreated, ultimately results in brainstem compression, ischaemia, haemorrhage and death. Created with *Biorender.com*.

hyperreflexia and clonus. Such findings are more prevalent in HE in ALF than in cirrhosis, where hypotonia and hyporeflexia are more frequent.[87] Regular evaluation for signs of ICH should be performed in patients with grade 3–4 HE, with sudden onset systemic hypertension, changes in pupillary reactivity, abnormal oculovestibular reflexes and/or decerebrate posturing indicating raised ICP.[77]

Measurement of arterial ammonia concentration is valuable; arterial ammonia concentrations of over 100 µmol/L predict progression to severe HE with 70% accuracy, and 55% of patients with ALF with an arterial ammonia concentration of over 200 µmol/L develop ICH.[88]

Transcranial Doppler ultrasound measures middle cerebral artery blood flow velocity and is a useful non-invasive ICP monitoring tool, which has now largely replaced invasive monitoring.[89] Reverse jugular vein oxygen saturation can also be monitored.[90] Measurement of optic nerve sheath diameter is also representative of ICP.[91] CT is helpful to exclude cerebral oedema and the presence of alternative cerebral pathologies.[92] EEG is not used to diagnose encephalopathy or cerebral oedema in this setting,[87] though it is useful to detect subclinical seizures if suspected.[77]

The disadvantage of most non-invasive methods is lack of continuous monitoring. Invasive ICP monitoring, involving insertion of an ICP sensor, most commonly in the extradural space, allows for continuous ICP evaluation, cerebral perfusion pressure (CPP) estimation and therefore management of pressure surges. However, studies have not demonstrated an effect on clinical outcome and the procedure carries considerable risk.[93–95] Therefore, invasive ICP monitoring is only recommended in a highly select subgroup of intubated and ventilated patients with ALF with grade 3–4 HE considered at high risk of ICH, based on the presence of one or more of the following variables; young patients with hyperacute or acute presentation, ammonia level over 150–200 µmol/L that does not decline with initial treatment (fluids and RRT), renal impairment and/or vasopressor support (>0.1 µg/kg/min).[8]

Prevention and treatment of hepatic encephalopathy and cerebral oedema

Intravenous N-acetylcysteine improves transplant-free survival and reduces length of stay in patients with non-paracetamol ALF with grade 1–2 HE, but is not efficacious in cases with grade 3–4 HE.[96 97] There is no

evidence base for treatment with rifaximin or disaccharides in the treatment of HE in ALF, and lactulose enemas are contraindicated due to the risk of increasing ICP.[70]

Preventative measures and treatment of cerebral oedema focus on preventing and treating infection, controlling inflammation, sufficient sedation and correcting hypo-osmolality.[77] If invasive monitoring is used, ICP should be maintained at less than 20 mm Hg and CPP over 50 mm Hg.[98] Nursing in the 30° head-up position favours venous drainage to reduce ICP while maintaining CPP. Nociceptive stimuli should be avoided, agitation controlled and propofol used to ease mechanical ventilation and reduce seizure risk.[77] Hyponatraemia should be corrected, and a serum sodium of between 145 and 150 mmol/L should be sustained to maintain the blood-brain barrier osmotic pressure gradient.[98] Temperature should be maintained at <37°C.[70]

Patients with ALF require adequate fluid resuscitation; plasma volume expansion reduces plasma ammonia by increasing urinary ammonia excretion.[98] However, fluid administration requires a cautious approach; fluid overload worsens cerebral oedema, increasing the risk of ICH and should be avoided.[70] Norepinephrine is the preferred vasopressor in patients with persistent hypotension, with vasopressin employed in refractory cases.[99] While respiratory failure is relatively uncommon in ALF, if ventilated, low tidal volumes should be used and hypercarbia and hypocarbia avoided.[6] Acute kidney injury is frequent, observed in 70% of cases[100] and associated with worse outcomes.[101] CRRT is preferable, given lower rates of cerebral oedema and haemodynamic instability.[102]

Use of CRRT leads to clinically meaningful reduction in circulating ammonia levels, and hyperammonaemia is a recognised indication for RRT in ALF, independent of renal function.[103 104] Early CRRT may improve transplant-free overall survival in ALF by averting hyperammonaemia and resultant complications.[104–106]

While early enteral nutrition should be employed, in patients with high arterial ammonia levels at risk of cerebral oedema, nutritional therapy can be delayed for 24–48 hours until hyperammonaemia is controlled. Arterial ammonia should then be monitored once nutritional protein support is started.[29] Hypoglycaemia, due to impaired gluconeogenesis, glycogenolysis and reduced hepatic glycogen stores, worsens HE and glycaemia should be monitored a minimum of 6 hourly.[81]

A high level of clinical suspicion for the presence of bacterial and/or fungal infection should be maintained, with a low threshold for empirical broad-spectrum antibiotics and antifungal therapy, especially in those with prolonged organ support.[107] Multidrug-resistant infections are associated with an increased incidence of grade 3–4 HE.[108]

Treatment of intracranial hypertension

First-line treatment of ICH is osmotic therapy with hypertonic saline or mannitol. Sustained surges in ICP (>25 mm Hg) or advent of clinical signs suggestive of elevated ICP should be treated with a bolus of hypertonic saline (200 mL 2.7%, or 20 mL 30%)[107] or intravenous mannitol (150 mL 20%),[109] while ensuring adequate sedation. Short-term hyperventilation, reducing arterial carbon dioxide pressure to 25–30 mm Hg, causes precapillary vasoconstriction, decreasing cerebral blood flow and can be employed to transiently reduce ICP if osmotic therapy has not had a sufficient effect.[8] CRRT should be used when serum ammonia is over 150–200 µmol/L,[70] aiming to maintain serum ammonia <100 µmol/L and to sustain serum osmolarity under 320 milliosmoles.

Second-line treatments for refractory cases include induction of moderate hypothermia (central temperature of 33–34°C)[110 111] and use of barbiturates.[70] In patients with cerebral hyperaemia and persistent ICH, a bolus of intravenous indomethacin, which induces cerebral vasoconstriction, has been used (0.5 mg/kg).[112]

Emergency hepatectomy may be conducted in some centres as a bridge to emergency LT, in cases of uncontrolled ICH and toxic liver due to massive necrosis.[8 113]

Liver support systems

Albumin dialysis systems, such as MARS and Prometheus, remove water-soluble and albumin-bound toxins, which accumulate and stimulate hepatic and systemic inflammation, and may support hepatic function.[114] MARS has been demonstrated to improve biochemistry and haemodynamic instability in ALF,[115 116] but without impact on survival and therefore such systems are not advised outside of the research setting.[117]

TPE is the only liver support treatment available and recommended for treatment of ALF in current guidelines, either as a bridge to LT or native organ recovery or when LT is contraindicated.[8 118 119] Several studies have demonstrated that high volume TPE is associated with improved transplant-free survival, alongside improving the grade of HE and decreasing vasopressor requirements.[119–121] Its mechanism of action is attributed to dampening of the innate immune response, amelioration of multiorgan dysfunction[121] and increased hepatic urea synthesis.[120] However, a recent retrospective real-world cohort study of 378 patients with ALF, 120 of whom received TPE, demonstrated significant improvement in haemodynamic status in those receiving TPE, but did not confirm survival benefit.[122]

Liver transplantation for ALF

The ultimate treatment for ALF is emergency LT, which is indicated in those in whom adequate regeneration will not occur and death is therefore inevitable.[8]

The most widely used prognostic criteria for LT in ALF are the King's College criteria introduced in 1989,[123] which mandate the presence of HE, originally derived and validated from two retrospective cohorts of patients with ALF treated without LT. The LT selection criteria in the UK have since been revised, and now have seven categories.[124]

LT reverses cerebral oedema and HE, though a number of neurological manifestations, including seizures and intracranial haemorrhage, may still occur postoperatively.[77] With good graft function, ICH should resolve 48 hours post-LT.[125 126]

CONCLUSION

The inpatient management of HE differs depending on grade, precipitant and underlying aetiology. Clinician familiarity with this management is imperative to ensure optimal care of patients with acute decompensation, ACLF and ALF. Healthcare providers must be vigilant to the development of grade 3–4 HE and need for ICU admission, and specialist LT centre referral where indicated.

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